Pulmonary Metastasectomy for Melanoma

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Abstract: After primary tumor treatment, 30% of patients with malignant melanoma develop metastatic disease, usually associated with a poor prognosis. Effective chemotherapeutic regimens for metastatic melanoma are not currently available. Surgical treatment of pulmonary metastases remains controversial because of the dismal survival rates reported in several studies. However, for patients with good performance status, long disease-free interval, limited metastatic disease, and less aggressive tumor biology, it remains an option. The authors have analyzed their experience in 26 patients operated on between 2000 and 2008 alongside a review of the large series in the literature.

Key Words: Melanoma, Pulmonary metastasectomy.

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After primary tumor treatment, 30% of patients with malignant melanoma develop metastatic disease, usually associated with a poor prognosis. Despite the impressive therapeutic advances that have been made during the last three decades for early stage melanoma, prognosis of metastatic disease remains poor. Chemotherapy and biotherapy have demonstrated only partial clinical response. The regimens, either alone or in combination, are usually difficult to tolerate and dramatically impact on patients' quality of life and provide little, if any, proven survival benefit.[1] In contrast, surgical resection of pulmonary metastases may be considered a safe and effective approach. In highly selected cases, metastasectomy may be followed by long-term survival. In the absence of better systemic treatments, we as thoracic surgeons are prevailed on to offer our help to these patients. We sought to review our practice and results in the light of the evidence from large datasets.

OUR INSTITUTIONAL EXPERIENCE

We present our experience, which we believe to be representative of the approach undertaken by a dedicated high-volume thoracic surgical team with experience of pulmonary metastasectomy for a range of primary diagnoses. From January 2000 to December 2008, 26 patients with stage IV melanoma underwent surgical resection of lung metastasis (mean age 62 years, range 28–79 years) at the Department of Thoracic Surgery of University of Torino (Table 1).

There were 14 men and 12 women. Three patients underwent a repeat complete metastasectomy. Eligibility criteria for curative resection included complete resection of the primary tumor, no evidence of extrapulmonary metastases, resectable pulmonary metastasis, and predicted postresection lung volumes compatible with the anticipated resection. Complete tumor resection was confirmed histologically in all cases. A retrospective study was performed to analyze clinical outcome and survival time. In 17 patients (65%), the lung represented the first metastatic localization, and in nine patients (35%), pulmonary metastases developed after metastatic spread to extrapulmonary sites. Fourteen patients presented with a single pulmonary metastases, five patients had two lesions, and seven patients had three or more lung metastases. All patients in the study received adjuvant or neoadjuvant systemic therapy. The median time interval from surgery for the primary tumor to resection of lung metastases was 36 months (range 12–240 months). In all cases, pulmonary metastases were discovered by chest radiography during a routine follow-up program. The mean tumor size was 15 mm ranging from <10 to 55 mm. An anatomic resection (lobectomy) was required in three patients, and the other 23

TABLE 1. Demographic and Clinical Characteristics of Patients (n = 26)

Gender (males/females)	14/12
Mean age (yr)	62 (range 28–79)
<40	4
40–60	8
>60	14
Lung localization	
Right lung	16
Left lung	8
Bilateral	2
No. of metastases	
1 Node	14
2 Nodes	5
>2 Nodes	7
Type of resection	
Wedge resection	23
Lobectomy	3
Median disease-free interval	36 mo

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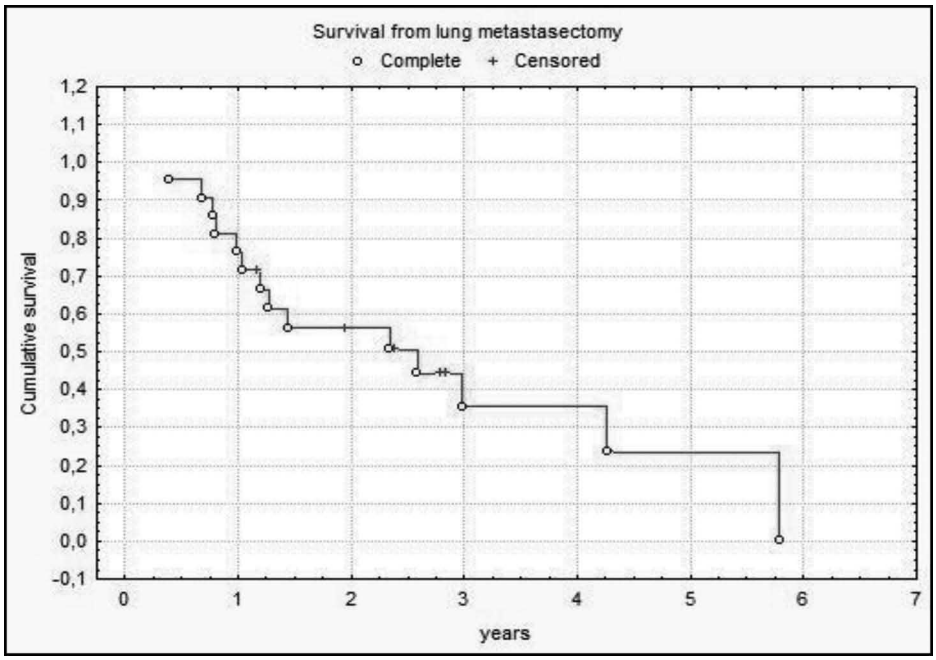

FIGURE 1. Overall survival.

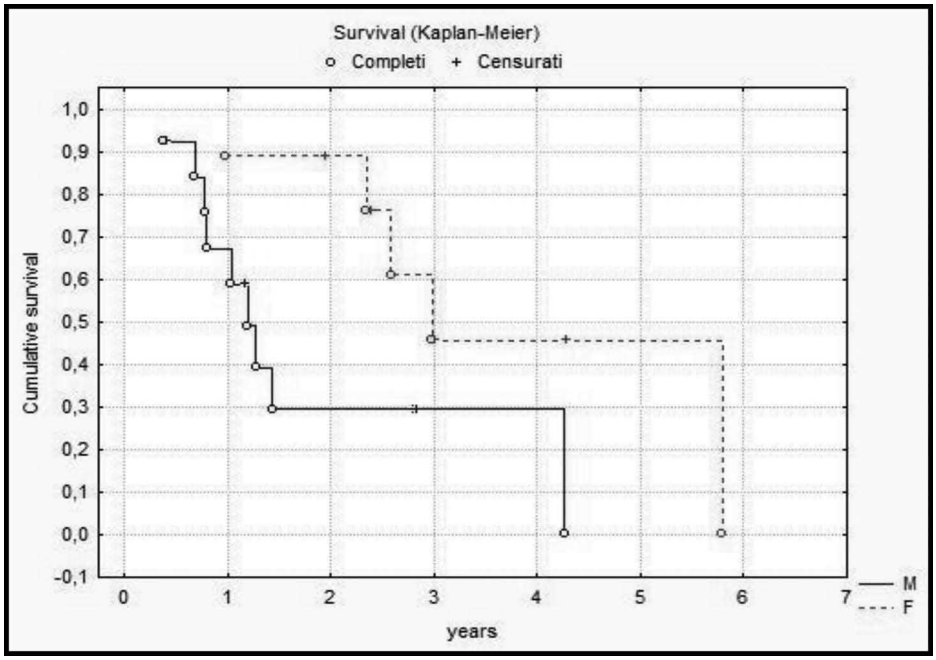

FIGURE 2. Survival and gender.

(88%) patients were treated with a wedge resection. There was no postoperative mortality.

Survival time was calculated from the date of surgical resection to the date of death or the last follow-up. The 1-, 3-, and 4-year survival rates are 72, 36, and 23%, respectively. Actuarial survival curves were calculated by the Kaplan-Meier method. Cox regression analysis was performed to identify independently predictive prognostic factors. We looked for the effect of age, sex, the number of metastases, and the interval from primary melanoma resection to lung metastasectomy on survival but only the female gender was independently a favorable factor for survival ($P = 0.05$; Figures 1–5). However, given the relatively small dataset and prior selection for these factors, failure to show effects of the number of metastases and the time interval may well be simply a matter of insufficient data to show a relationship.

REVIEW OF EVIDENCE FROM LARGE SERIES

A formal search of the literature reveals many case reports of unusual manifestations and some small series. We selected three case series for presentation in our evidence

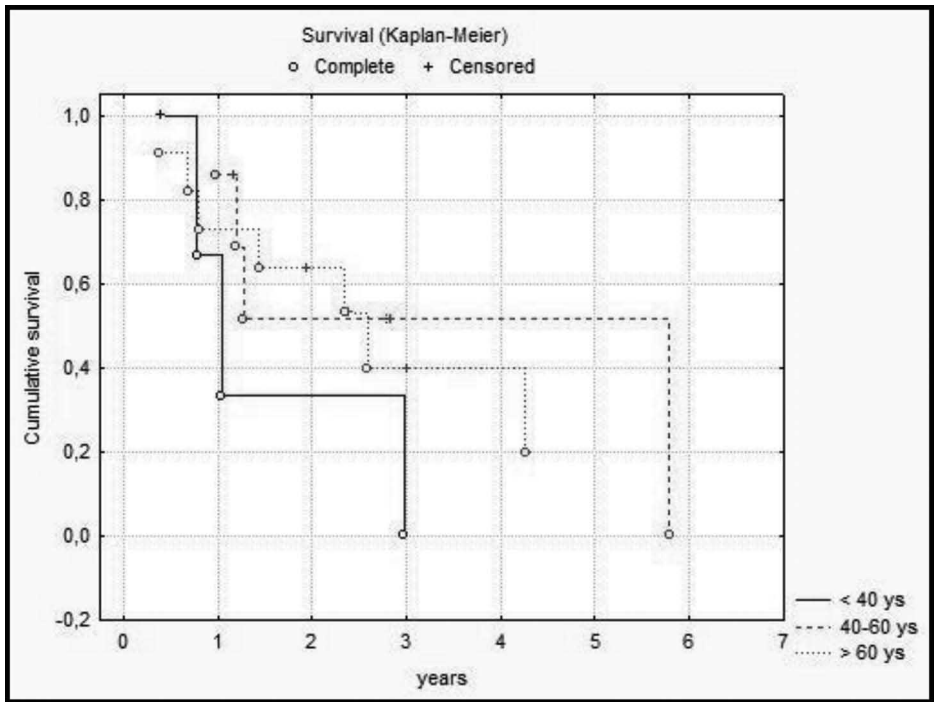

FIGURE 3. Survival and age.

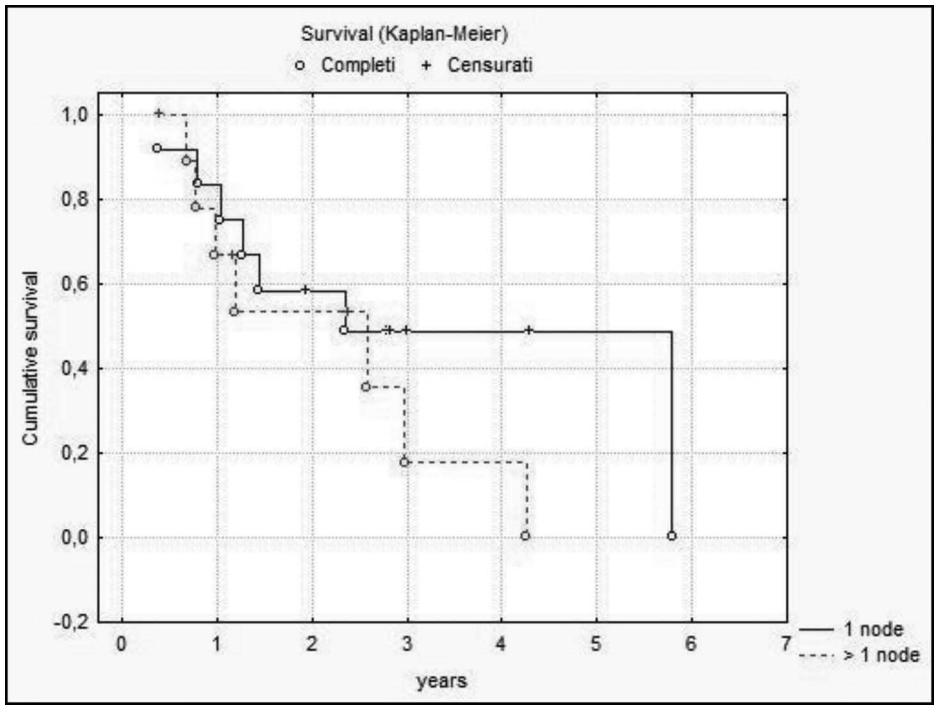

FIGURE 4. Survival and number of nodes.

table on the basis of their size, some information concerning the size of the denominator from which the cases were selected, and the applicability of the data and its analysis to our clinical context[1–3] (Table 2).

Tafra et al.[2] reviewed a 22-year melanoma database of 6100 patients. Of 984 patients with pulmonary metastases, 106 underwent surgical treatment; the remaining 878 cases were treated with immunotherapy, chemotherapy, radiotherapy, or a combination. The 1-, 3-, and 5-year survival rates for surgical patients were 77, 37, and 27% compared with 32, 7, and 3% in nonsurgical patients, respectively. The highest 5-year survival rate (39%) occurred in patients with a single metastatic lesion (Table 3).

Pastorino et al.[3] reported melanoma outcomes within the International Registry of Lung Metastasectomy in 328 patients who underwent lung metastasectomy in the period

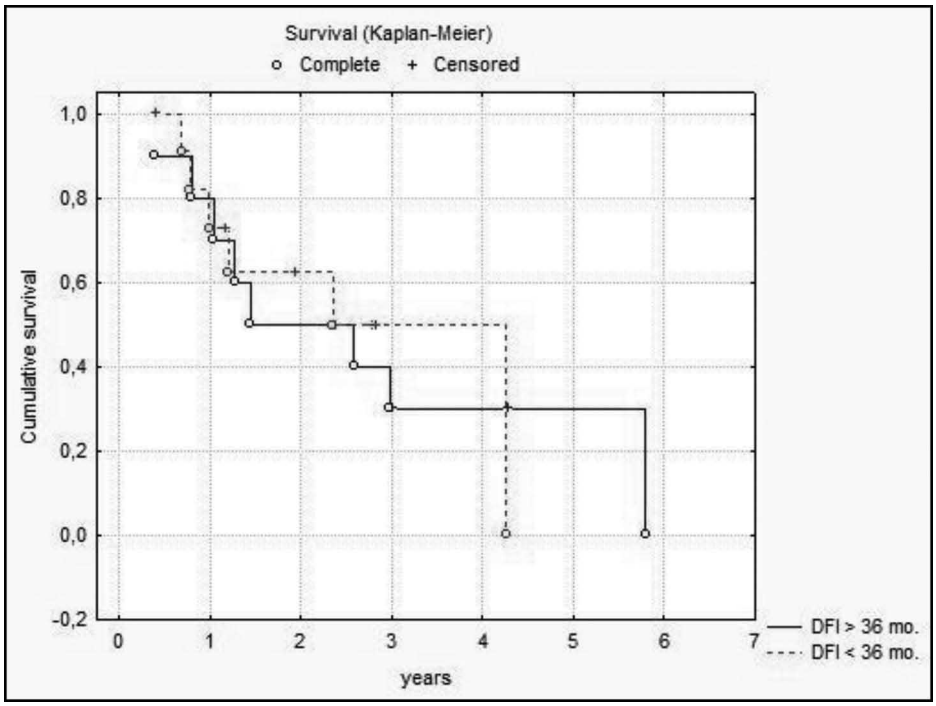

FIGURE 5. Survival and disease-free interval (DFI).

TABLE 2. Data from Three Reports Including Pulmonary Metastasectomy for Melanoma

Study/Report	Period	Melanoma Patients in the Database/Registry	Pulmonary Metastases	Pulmonary Metastasectomy	Operative Rate	5-yr Survival Rate	10-yr Survival Rate
Tafra et al.[2]	1971–1993	6100	984	106	11%	27%	
Pastorino et al.[3]	1945–1995			328		22%	16%
Petersen et al.[1]	1970–2004	14,057	1720	298	17%		

Where data were available, the total number of melanoma cases in the registry is given (Column 3), the number of patients with pulmonary metastases, the total number, and the percentage that had metastasectomy are given in Columns 4–6.

TABLE 3. Univariate and Multivariate Analyses of Factors Affecting Survival of Surgical Patients

Factor	Univariate	Multivariate
Tumor doubling time (<60 vs. >60 d)	0.0005	0.002
Presence of extrapulmonary metastases	0.014	0.04
No. of lung metastases (1 vs. >1)	0.006	0.9
Complete vs. incomplete resection	0.09	
Wedge resection vs. lobectomy	0.13	
Disease-free interval (30 vs. >30 mo)	0.315	

Data from Tafra et al.[2]

TABLE 4. Hazard Ratios for Factors Predictive of Overall Survival in Patients with Pulmonary Metastases

Predictor	Hazard Ratio	95% Confidence Interval	*p*
Nodular histologic type	1.1	1.01–1.3	0.033
No. of pulmonary metastases <2	1.2	1.04–1.4	0.012
Disease-free interval	1.5	1.3–1.7	<0.001
Presence of extrathoracic metastasis	1.7	1.6–1.9	<0.001
Pulmonary metastasectomy	0.5	0.4–0.6	<0.001

Reference category is disease-free interval longer than 5 yr.

1945 to 1995. After complete surgical resection, the 5- and 10-year survival rates were 22 and 16%, respectively. A disease-free interval shorter than 36 months and the presence of multiple metastases were independent unfavorable prognostic factors. There were no long-term survivors after incomplete resection.

The report of Harpole et al.[4] in 1992 has been updated with a recent report of 1720 patients with pulmonary metastases from a database of 14,057 patients collected during the period 1970 to 2004. From the large databases of all melanoma cases, the 5-year survival rate for patients with metastases was approximately 6%. Favorable predictors for survival are given in Table 4. Given that pulmonary metastasectomy features among them, it is not surprising that patients and their oncologists seek the help of thoracic surgeons.

Recently, Neuman et al.[5] claimed 3-fold difference in median survival with and without pulmonary metastasectomy. They presented a series of 122 patients with stage IV

melanoma and pulmonary metastasis as the initial disease site; median survival was 14 months. Of these, 26 (21%) underwent metastasectomy, with a median survival of 40 months compared with 13 months in patients not selected for surgical treatment. Clinical factors at the time of diagnosis of stage IV melanoma independently predictive of survival were a solitary pulmonary metastasis ($P < 0.0005$) and the absence of extrapulmonary disease ($P = 0.01$).

Finally, Ollila et al.[6] presented an experience of 129 patients undergoing complete or partial resection of lung metastatic melanoma. They identified the tumor doubling time (TDT) as the most significant preoperative prognostic factor for patients undergoing pulmonary metastasectomy. For TDT <60 days, neoadjuvant chemotherapy is recommended. Their conclusion is that pulmonary metastasectomy should not be attempted if TDT cannot be increased over 60 days by the systemic therapy.

DISCUSSION

When denominator data are available, it is first important to note the high degree of selection for pulmonary metastasectomy of patients with metastases, which is 11 and 17% (Table 2). That said, *pro rata*, it seems that pulmonary metastasectomy is much more commonly performed in patients with melanoma than those with colorectal cancer where the equivalent rate is of the order of 1 to 2%.[7,8] Direct comparison of outcomes in the selected patients with those selected to not have surgery is clearly not appropriate. Naturally correction must be applied, but adjustment can only be made for known factors that have been recorded in the database. Many factors go into the selection of patients for surgery, by themselves, and at primary, secondary, and tertiary care, which cannot be captured. When the degree of selection is of the order of 1 in 5–10, it would not be surprising if there is more in the expert selection that is performed than can be captured by the statistical techniques employed.

There is also some concern about the selective reporting of patients in whom complete resection was performed.[1,3] The criteria on which we select future patients have to be those which are available to clinicians at the time of decision making. Reporting the outcomes on "intention to treat" should include patients where, despite best intentions, R0 resection was not achieved. That should be included in the headline outcome data and is what future patients need to know.

It is clear that all the factors associated with longer survival in patients undergoing metastasectomy are also predictors of longer survival in the disease overall including TDT. We still cannot be sure whether the selection of cases with these features is the explanation for longer survival in patients undergoing pulmonary metastasectomy.[9] A consistent feature is that complete removal of all disease versus incomplete removal is associated with a significant difference in survival[10] cannot ignore the evidence that patients who have presented with few lesions, usually a single metastasis, may be long survivors after complete removal and will continue to ask for surgery in the hope case that surgery will have a beneficial effect on their survival. Conversely, there is increasingly strong evidence of the factors that predict poor survival after surgery, and so, we will want to continue being highly selective.

RECOMMENDATIONS

Our conclusion for future practice is that pulmonary metastases from malignant melanoma should be operated if the patient meets the following criteria:

1. The primary site of melanoma is fully controlled.
2. There is a limited number of pulmonary metastases.
3. There is no evidence of extrapulmonary metastases in computed tomography and positron emission tomography-computed tomography scans.
4. A long disease-free interval has passed by between the resection of the primary melanoma and the development of pulmonary metastasis.
5. A presumably complete resection of the lung metastases can be accomplished.
6. There is no clinical and imaging evidence of involvement of intrathoracic lymph nodes.
7. A long TDT is identified.

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